

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 17 JAN 2007		
Applicant's or agent's file reference 27797		
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/IL04/00335	International filing date (day/month/year) 18 April 2004 (18.04.2004)	Priority date (day/month/year) 02 June 2003 (02.06.2003)
International Patent Classification (IPC) or both national classification and IPC IPC: C12N 9/26(2007.01);A61K 38/00(2007.01),38/47(2007.01) USPC: 435/201;514/2;424/94.61		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD.		

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input checked="" type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

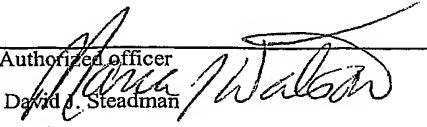
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 14 December 2006 (14.12.2006)	Authorized officer  David J. Steadman Telephone No. 571-272-1600
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☒ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☒ on paper
- ☒ in electronic form

c. time of filing/furnishing

- ☒ contained in the international application as filed.
- ☒ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-8,33-54,57-75,87-97, reciting Table 4 and SEQ ID NO:1

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>4,7-8,38-54,87-97</u>	YES
	Claims <u>1-3,5-6,33-37,57-75</u>	NO
Inventive step (IS)	Claims <u>4,7-8,38-54</u>	YES
	Claims <u>1-3,5-6,33-37,57-75,87-97</u>	NO
Industrial applicability (IA)	Claims <u>1-8,33-54,57-75,87-97</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-3, 5-6, 33-37, and 57-75 lack novelty under PCT Article 33(2) as being anticipated by Roeber et al. (*Acta Crystallogr D Biol Crystallogr* 59D:343-344, 2003), which teaches: 1) Ceredase and Cerezyme, which are disclosed as being recombinant human beta-glucocerebrosidase used clinically for treatment of Gaucher's disease; 2) a crystal of a recombinant human glucocerebrosidase having orthorhombic space group C2221 and unit cell parameters a=285.0, b=110.2, c=91.7 Angstroms and diffracts X-rays to a resolution of 2.75 Angstroms; and 3) a method of making said crystal.

Claims 87-97 lack an inventive step under PCT Article 33(3) as being obvious over Roeber et al., which, as noted above, teaches Ceredase and Cerezyme, which are disclosed as being recombinant human beta-glucocerebrosidase used clinically for treatment of Gaucher's disease. In view of the teachings of Roeber et al. the "article of manufacture" according to claims 87-97 would have been obvious.

Claims 4, 7-8, 38-54 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed invention.

Claims 1-8, 33-54, 57-75, and 87-97 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-8, 33-54, 57-75, and 87-97 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The application, as originally filed, did not describe: all crystals, methods of making, pharmaceutical compositions, and articles of manufacture as encompassed by the claims. In this case, the disclosure of the single polypeptide, crystal thereof, and method of making said crystal fail to describe all crystals, methods of making, pharmaceutical compositions, and articles of manufacture as encompassed by the claims.

Claims 1-8, 33-54, 57-75, and 87-97 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: the disclosure of the single polypeptide, crystal thereof, and method of making said crystal fails to enable one to make all crystals, methods of making, pharmaceutical compositions, and articles of manufacture as encompassed by the claims.